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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/772,768	02/04/2004	David A. Horwitz	067797-5006-US01	2359

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EXAMINER	
JUEDES, AMY E	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/772,768	HORWITZ, DAVID A.	
	Examiner	Art Unit	
	Amy E. Juedes, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 6/11/07 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/11/07 has been entered.

Claims 1-6 are pending and are under examination.

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1-3 and 6 stand rejected under 35 U.S.C. 102 (e) as being anticipated by U.S. Patent No: 6,685,936 (of record).

As set forth previously, The '936 Patent teaches suppressor T cells capable of treating (i.e. decreasing) transplant rejection (see in particular column 3, lines 14-15). Further, '936 Patent teaches suppressor T cells to be CD8+ T cells (see in particular column 8, lines 23-24). However, the '936 Patent does not teach the same process of making the claimed suppressor T cells. As regards to applicant's reliance upon product-by-process limitations within the claimed methods; it is noted that the patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985) See MPEP 2113. The claimed compound is the same compound as taught by the '936 patent irrespective of how it is made.

Applicant's arguments and declaration of inventor Horwitz, filed 6/11/07, have been fully considered, but they are not persuasive.

Applicant argues that in contrast to the cells of the '936 patent, the presence of CD8+ T cells is not required for the suppressor activity exhibited by the claimed CD4+ cells.

The instant claims are not limited to CD4+ cells, as asserted by Applicant. In fact, the instant claims specifically encompass a population of suppressor T cells generated by culturing enriched CD8+ T cells. It is unclear how said suppressor cells could possibly be "independent of CD8+ T cells", when in fact they require CD8+ T cells as a starting material. The '936 patent teaches a population of CD8+ suppressor T cells capable of decreasing graft rejection, and thus meets all the limitations of the instant claims.

Applicant further argues that, as evidenced by Batten et al., T cells stimulated by mesenchymal stem cells display a different cytokine profiles than T cells cultured with PBMCs. Thus, Applicant concludes that the suppressor cells produced by the method of the '936 patent involving culture with mesenchymal stem cells are different than the instant cells which are produced by culture with PBMCs.

Batten et al. demonstrate that in contrast to the Th1 cytokine profile displayed by PBMCs cultured with allogenic PBMCs, PBMCs stimulated with mesenchymal stem cells display a regulatory phenotype (i.e. are suppressor cells, as recited in the instant claims). Batten et al. do not compare PBMCs cultured with mesenchymal stem cells with the cells of the instant claims (i.e. PBMC cultured with irradiated T cell depleted mononuclear cells and TGF-β). Therefore, Applicant has not provided any evidence that the instant cells differ from the cells disclosed by the '936 patent.

Applicant further argues that the claimed suppressor cells are CD8+CD28+Foxp3+, and are thus not identical to the cells taught by the '936 patent. Applicant further provides a declaration by Inventor Horwitz, which provides evidence of the expression of FoxP3, and further states that since naïve CD8+ T cells are used as the starting population in the present invention, the cells of the instant claims are CD28+.

As an initial matter, it is noted that the instant claims are not limited to suppressor cells that are CD8+CD28+FoxP3+. In fact, Applicant has specifically argued that the claimed suppressor cells do not require the presence of CD8+ T cells.

Regarding CD28 expression, Applicant cites a journal article demonstrating that naïve CD8 T cells express CD28. However, the instant claims are not limited to suppressor T cells generated using naïve CD8 T cells as a starting material, as asserted by Applicant. Furthermore, even if the claims were limited to employing a starting material that expresses CD28, this does not necessarily ensure that the end product after culture expresses CD28. Applicant has not provided any evidence that the cells of the instant claims express CD28. Furthermore, regarding FoxP3, the evidence provided by Applicant indicates that CD8+CD28+ T cells cultured with anti-CD3, anti-CD28, IL-2, and TGF-β express FoxP3. Applicant has not provided any evidence that the cells of the instant claims (i.e. PBMC cultured with irradiated T cell depleted PBMC and TGF-β) express FoxP3. Furthermore, the article cited by Batten et al. demonstrates that PBMC cultured with mesenchymal stem cells express FoxP3. Therefore, based on Applicant's evidence, the cells of the '936 patent that are generated by culture with mesenchymal stem cells do express FoxP3.

4. Claims 1-5 stand rejected under 35 U.S.C. 102 (b) as being anticipated by Hall et al. (of record).

As set forth previously, Hall et al. teach CD4+ suppressor T cells capable of inhibiting restoration of transplant rejection (i.e. decreasing transplant rejection) (see in particular page 154, Summary, lines 7-8). Additionally, Hall et al. teach CD4+ suppressor T cells to be CD45R (see in particular page 152, 2nd paragraph, line 1) and that $CD45R^+$ cells to be naïve cells (i.e. naïve CD4+ T cells) (see in particular page 152, 2nd paragraph, lines 14-15). However, Hall et al. do not teach the same process of making the claimed suppressor T cells. As regards to applicant's reliance upon product-by-process limitations within the claimed methods; it is noted that the patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985) See MPEP 2113. The claimed compound is the same compound as taught by Hall et al., irrespective of how it is made.

Applicant's arguments and declaration, filed 6/11/07, have been fully considered, but they are not persuasive.

Applicant argues that the cells taught by Hall et al. require CD8+ T cells to mediate their suppressive effect, while the instant cells exhibit suppressive activity independent of CD8+ T cells, as evidenced by Exhibit 4 (Zheng et al.).

The instant claims are not limited to suppressor T cells that mediate suppression independent of CD8 T cells. In fact, as noted above, Applicant concedes that the instant claims encompass CD8+ suppressor T cells. It is unclear how a

suppressor T cell that is itself CD8+ can act independently of CD8+ T cells (i.e. independently of itself). Furthermore, the journal article cited by Applicant as exhibit 4 (Zheng et al.) describes a population of regulatory T cells produced by simulating CD4+ T cells with SEB and TGF-β. Applicant has not provided any evidence that suppressor T cells produced by the claimed method (i.e. culture with irradiated T cell depleted PBMC and TGF-β) exhibit suppressive activity independent of CD8+ T cells. Furthermore, the cells taught by Hall et al. do mediate suppression independent of CD8 T cells (see Table V, transfer of suppressor T cells into irradiated OxB treated hosts prolongs graft survival to a median of 38 days, compared to 16.5 days in the absence of suppressor cells).

Applicant further argues that the cells of the instant invention express Foxp3, and that cyclosporine (which is administered in the method of Hall et al.) compromises the generation of cells expressing Foxp3. Thus, Applicant concludes that the method of Hall et al. produces a different population of cells than the instant method.

The instant claims are not limited to FoxP3 expressing suppressor T cells. In addition, the evidence provided by Applicant indicates that CD8+CD28+ T cells cultured with anti-CD3, anti-CD28, IL-2, and TGF-β express FoxP3. Applicant has not provided any evidence that the cells of the instant claims (i.e. PBMC cultured with irradiated T cell depleted PBMC and TGF-β) express FoxP3.

5. The following are new grounds of rejection.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Groux et al., 1997, in view of Seder et al., 1998.

Groux et al. teach a population of regulatory T cells (i.e. suppressor T cells) made by incubating a CD4+ enriched population of PBMC with irradiated allogenic monocytes (i.e. a donor population of mononuclear cells depleted of T cells, see page 739 in particular). Groux et al. also teach that the suppressive activity of the cells is mediated by their production of TGF-β (see page 70 in particular).

Groux et al. do not teach incubating the CD4+ T cells with TGF-β.

Seder et al. teach that incubating CD4+ T cells with TGF-β enhances the production of TGF-β by the T cells.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add TGF-β, as taught by Seder et al. to the cultures of regulatory T cells taught by Groux et al. The ordinary artisan at the time the invention was made would have been motivated to do so in order to enhance TGF-β production by the regulatory T cells, since Groux et al. teach that the suppressive activity of the regulatory T cells is mediated by their production of TGF-β, and Seder et al. teach that culture with TGF-β enhances TGF-β production by T cells. Furthermore, claim 5 is included since PBMC enriched for CD4+ cells are enriched for naïve CD4+ T cells compared to the starting population of PBMC. Claim 3 is included since the patentability of a product does not depend on its method of production, and Groux et al. and Seder et al. make obvious the suppressor T cells of the instant claims.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, Ph.D. whose telephone number is 571-272-4471. The examiner can normally be reached on 8am - 5pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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7/18/07
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